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Identification of novel genetic markers and improved treatment options for diabetic kidney disease

“...genetic risk assessment, in combination with clinical factors, will provide a noninvasive approach to assess disease stage, predict response to pharmacological intervention and evaluate propensity for disease progression.”

KEYWORDS: diabetes ■ end-stage renal disease ■ exome sequencing ■ genetics ■ genome-wide association studies ■ microvascular complications ■ nephropathy ■ personalized medicine ■ pharmacogenetics ■ RNA sequencing

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Diabetic nephropathy, a kidney disease that develops secondary to diabetes mellitus, accounts for most of the reduced life expectancy in individuals with diabetes and is the most common cause of chronic renal failure in developed countries [1]. In its early stages of development, diabetic kidney disease has no symptoms, and is characterized by a reduced glomerular filtration rate and atypical excretion of protein into the urine (i.e., microalbuminuria: 150–300 mg/day). In approximately 20–40% of individuals with diabetes, microalbuminuria progresses to overt nephropathy (urinary protein excretion >300 mg/day) and eventually culminates in end-stage renal disease (ESRD), where renal replacement therapy is necessary to control uremia and other metabolic consequences of kidney failure. ESRD is associated with substantial mortality and economic costs. In the USA alone, mortality rates are approximately 23% per year and nearly 400,000 people receive renal replacement therapy as a result of ESRD, incurring direct medical costs in excess of US\$16 billion annually [2]. Unsurprisingly, diabetic kidney disease presents a major public health concern in countries with burgeoning rates of diabetes.

At present, there is no cure for diabetic nephropathy; instead, current treatment strategies focus on prevention or delay of disease development and progression. In the early stages of diabetic kidney disease, lifestyle modification (i.e., maintenance of healthy weight, physical activity, dietary restriction of protein, salt and alcohol, avoidance of nonsteroidal anti-inflammatory drugs and smoking cessation), coupled with intensive pharmacological control of glycemia and blood pressure, are prescribed for most patients. However, following

progression to ESRD, treatment options become limited to dialysis and, ultimately, kidney transplantation. While current paradigms for clinical management of diabetic nephropathy are useful in delaying disease onset and preventing disease progression in some individuals, they do not do so for a significant proportion of diabetic individuals, who eventually end up developing more severe forms of nephropathy. Clearly, more advanced and efficacious pharmaceutical agents are urgently needed.

The precise causes of diabetic nephropathy are poorly understood. Duration of diabetes is one of the strongest determinants of kidney disease, although not every individual develops renal complications as a result of diabetes [3–5]. Other factors, such as glycemic control, hypertension, hyperlipidemia and cigarette smoking, also increase the risk of developing diabetic kidney disease; however, these determinants are relatively modifiable and efforts to control levels of glucose, blood pressure and lipids, and refrain from tobacco use, generally produce favorable effects on disease development and progression [6–10]. Nonetheless, many individuals develop diabetic nephropathy despite only relatively modest hyperglycemia, while other individuals who have suffered for many years of prolonged hyperglycemia, never develop nephropathy [11]. Furthermore, only one in 2500 patients with hypertension ever develops kidney disease [12]. These observations point toward other factors, such as genetic factors, which contribute to disease susceptibility, and it is now widely recognized that in individuals with diabetes, environmental and genetic factors, as well as interactions among them, largely determine individual risk for development and progression of kidney disease [13–15]. Without a doubt,

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the identification of genetic determinants for susceptibility to diabetic nephropathy and ESRD will lead to an enhanced understanding of the molecular mechanisms underlying disease pathology and, consequently, fuel the development of more advanced pharmacological therapies. Therefore, the link between genetic factors and diabetic kidney disease represents a critical area of focus in research endeavors for the development of diagnostic tools for early disease detection, and novel therapeutics targeting delay or prevention of disease progression.

Historically, two approaches have primarily been used to identify genes that mediate susceptibility to diabetic nephropathy. Linkage analysis is one approach that can be used to assess cosegregation of markers of the disease within families that have a confirmed history of diabetic nephropathy. The other strategy focuses on specific genes that encode proteins with known or suspected roles in the pathophysiology of diabetic nephropathy. In this approach, variants are typically identified within genes and the association of specific alleles with disease frequency is estimated. In addition, results from genome-wide association studies to identify loci for diabetic kidney disease are now becoming available in the literature [16–19]. Among the myriad of potential candidates identified using these various approaches, two genes – *CNDPI* and *ELMO1* – appear particularly promising based upon replication of association findings in independent studies and biological data supportive of their functional role in diabetic nephropathy. However, at present, the clinical relevance of these, as well as other findings, awaits additional validation and functional characterization to identify the molecular mechanisms by which these genes impact upon disease pathophysiology.

Despite the depth and diversity of research conducted to date, these studies still only represent the tip of the iceberg for identifying risk alleles for diabetic kidney disease. For example, the era of genome-wide association studies, while still relatively young, may nonetheless be shortly eclipsed by ‘next-generation’ sequencing [20]. Although next-generation sequencing of whole genomes or exomes is currently pricey, the cost of sequencing projects is quickly dropping and it is likely that this technology may soon become the standard approach for assessing human genetic variation. Sequencing provides rapid and accurate interrogation of more than 99% of the human genome. Furthermore, in some cases, rare variants of high penetrance

may contribute to disease risk and, to date, sequencing is the only technology that allows efficient identification of such variation [21]. The relatively new technique of RNA sequencing also offers an approach to reveal transcriptome profiles that are associated with disease progression and severity, and to delineate expression of novel quantitative trait loci that may, together with genotype data, reliably detect regulatory networks that will improve our understanding of the pathophysiology of diabetic nephropathy. These technologies, combined with those currently in development, will allow identification of genetic and genomic markers at a pace and economy not yet realized in this field.

There is no reliable way to predict which patients are most likely to develop diabetic nephropathy prior to the occurrence of actual metabolic changes in the kidney, nor can disease progression be prevented in a sizeable number of patients despite aggressive pharmacological treatment [22]. Therefore, there are three major ways that identification of novel genetic variants can be expected to lead to improvements in treatment strategies for diabetic kidney disease.

First, knowledge of risk alleles will enable earlier and more accurate methods for predicting which patients are at a greatest risk of developing more severe forms of the disease. As we know, some patients who develop microalbuminuria remain at this stage indefinitely, while others will progress at varying rates to nephropathy and ESRD. Knowing risk alleles for diabetic nephropathy, even in the absence of new pharmacological developments, will provide the impetus for intensive management of glycemia and blood pressure in high-risk individuals, which is expected to halt or prevent disease progression in a significant proportion of patients. In accordance, genetic tests could easily be developed as a marker panel assay that could economically and rapidly provide diagnostic clinical results.

Second, identification of risk alleles for diabetic nephropathy will help characterize novel gene pathways and networks of interest that could be targeted for drug development. Although inhibitors of the renin–angiotensin system are commonly used, well tolerated and generally efficacious options for managing diabetic kidney disease, they do not cure diabetic nephropathy, nor do they delay disease progression in all patients. Therefore, the need for more advanced and targeted pharmaceuticals is critical. Identification of genetic variants may lead to the consideration of novel pathways for drug

development to add to the present armamentarium of pharmacological agents for treatment of diabetic nephropathy.

Finally, genetic risk assessment, in combination with clinical factors, will provide a non-invasive approach to assess disease stage, predict response to pharmacological intervention and evaluate propensity for disease progression. Correspondingly, clinical management of disease will then take into consideration the molecular risk factors that constitute each patient's personal medical profile, which will lead to personalized treatment strategies to delay and, ultimately, prevent development of diabetic nephropathy.

Discovery of susceptibility genes and risk alleles for diabetic kidney disease will, thus, provide the basis for functional and epidemiological

studies to elucidate the mechanisms of disease pathogenesis and determine the population-level consequences of the variants. Such information is essential for efforts to address the substantial unmet clinical challenge of diabetic kidney disease care, given the growing burden of disease associated with diabetic ESRD and the need for improved therapeutic and preventive strategies.

Financial & competing interests disclosure

JK DiStefano is funded by the American Diabetes Association. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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